Particulate Handling in the Human Lung

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Overview

- The Human Lung and Lung Compartments
- Particles
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  - Characteristics that affect toxicity
- Particle Deposition
  - Mechanisms
  - Factors that affect particle deposition
- Particle Clearance
  - Mechanisms
  - Factors that affect particle clearance
- Metrics used to evaluate particle dose
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  - Volume
  - Surface area
- General Model of Particle Toxicity

The Human Lung

And

Lung Compartments

The Human Lung

5 lobes

2 left lobes

superior and inferior

3 right lobes

superior, middle, and inferior

Lung Compartments

Nasopharyngeal anterior nares to larynx

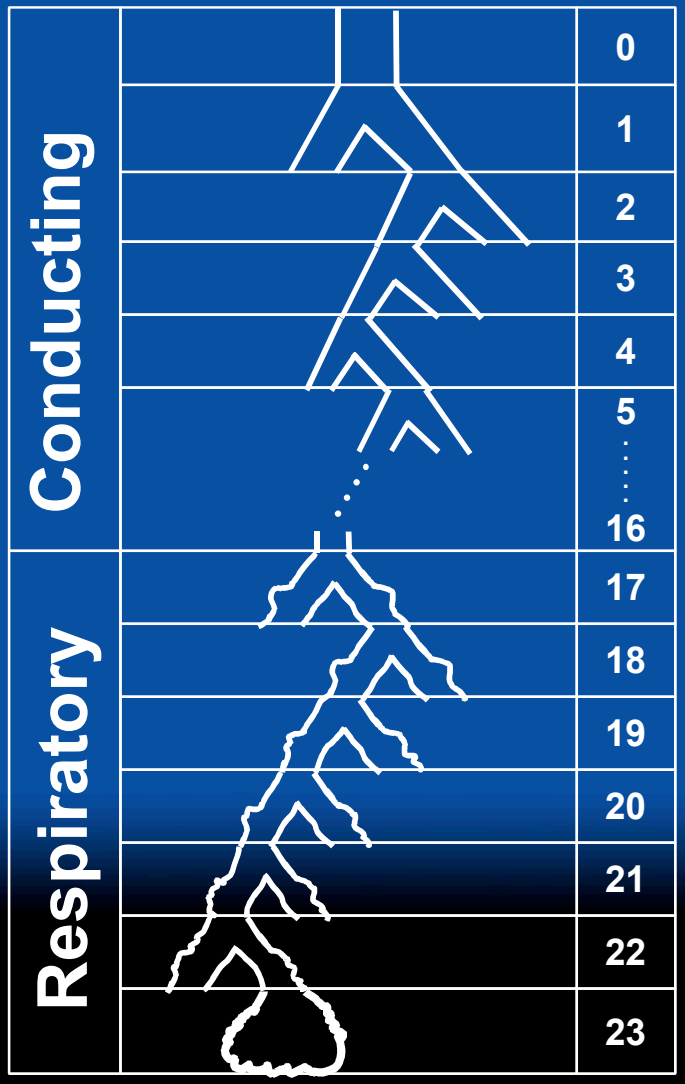
Tracheobronchial begins at larynx

- trachea
- bronchi
- bronchioles
- terminal bronchioles

Pulmonary

- respiratory bronchioles
- alveolar ducts
- alveoli

Architecture of the Tracheobronchial and Pulmonary Lung Compartments



Tracheobronchial compartment zones 1- 16

No gas exchange in this compartment.

Pulmonary compartment zones 17-23

Gas exchange occurs in this compartment.

Properties of Particles

Respirable Particle Nomenclature

Coarse particles > 2.5 μm

Fine particles 0.1-2.5 μm

Ultrafine (nano) particles 0.001-0.1 μm

Particle Characteristics that Affect Toxicity

Size - determines, in part, lung deposition

Solubility:

soluble particles - generally have low or no lung toxicity
can have systemic toxicity

insoluble particles – more likely to be toxic
exhibit a wide range of toxicities
dependent on other particle characteristics

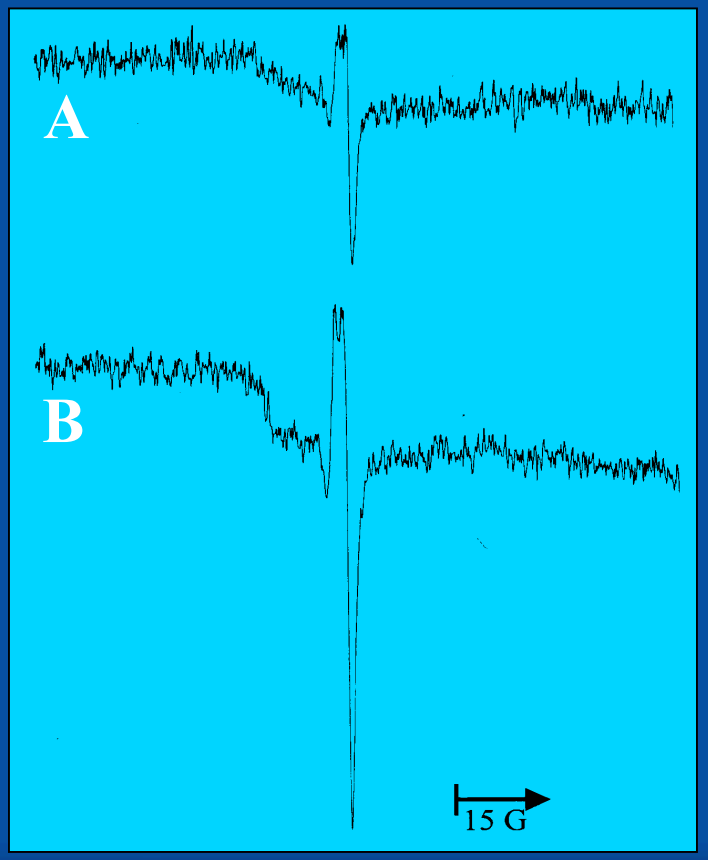
Particle Surface Chemistry Can Alter Toxicity

Surface Chemistry

A=aged silica
B=freshly fractured silica

ESR signal from freshly fractured silica is much greater than aged silica.

Freshly fractured silica is also more toxic.



Particle Deposition

Particle Deposition Mechanisms

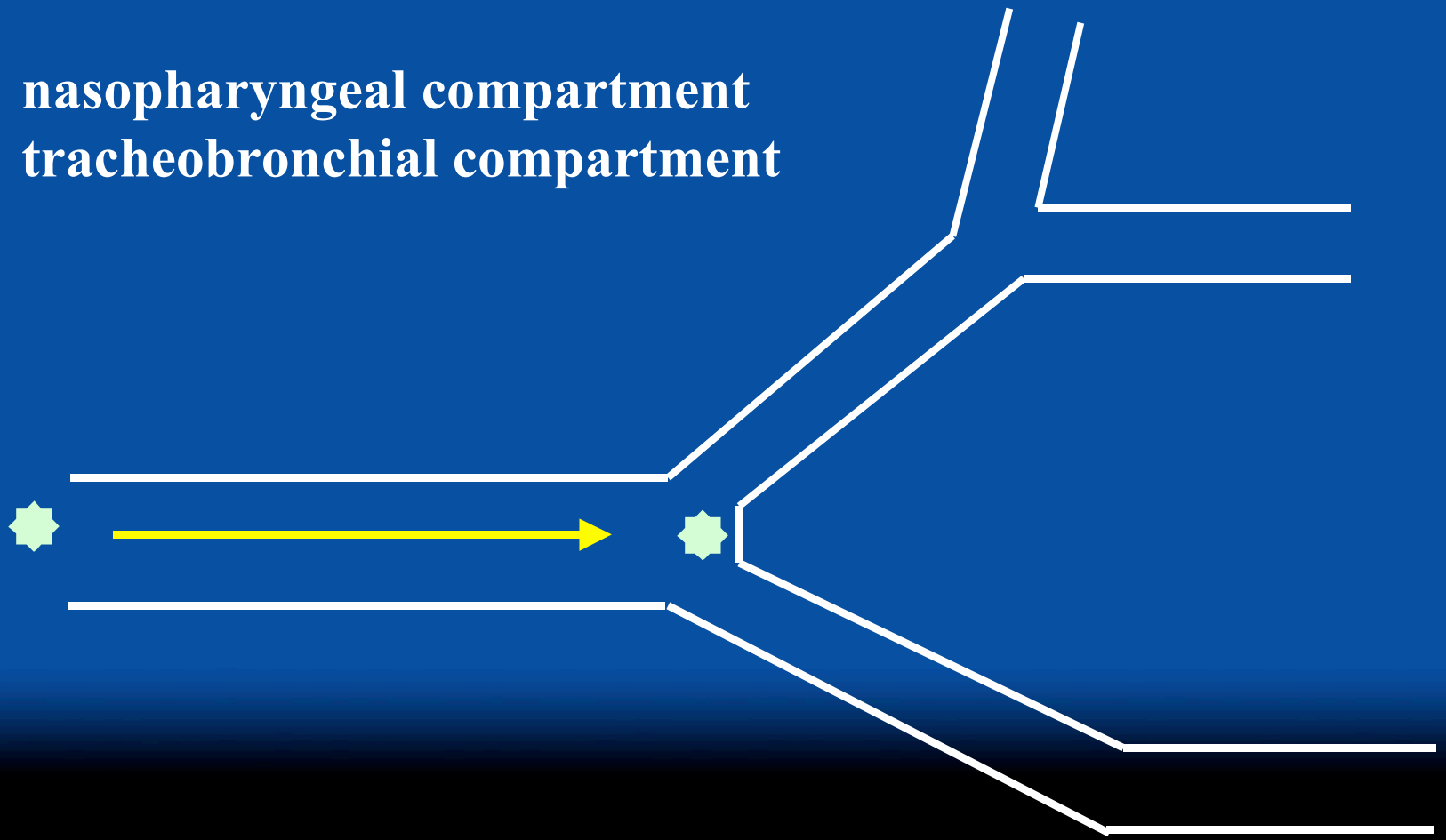
Nasopharyngeal	**impaction, sedimentation, electrostatic particles > 1 μm**
Tracheobronchial	**impaction, sedimentation, diffusion particles < 1 μm**
Pulmonary	**sedimentation, diffusion particles < 1 μm**

Airway branching pattern favors non-uniform (focal) areas of deposition, especially when impaction is an important deposition mechanism.

Impaction

The particle's momentum in air stream prevents it from making turn at a bifurcation.

nasopharyngeal compartment
tracheobronchial compartment

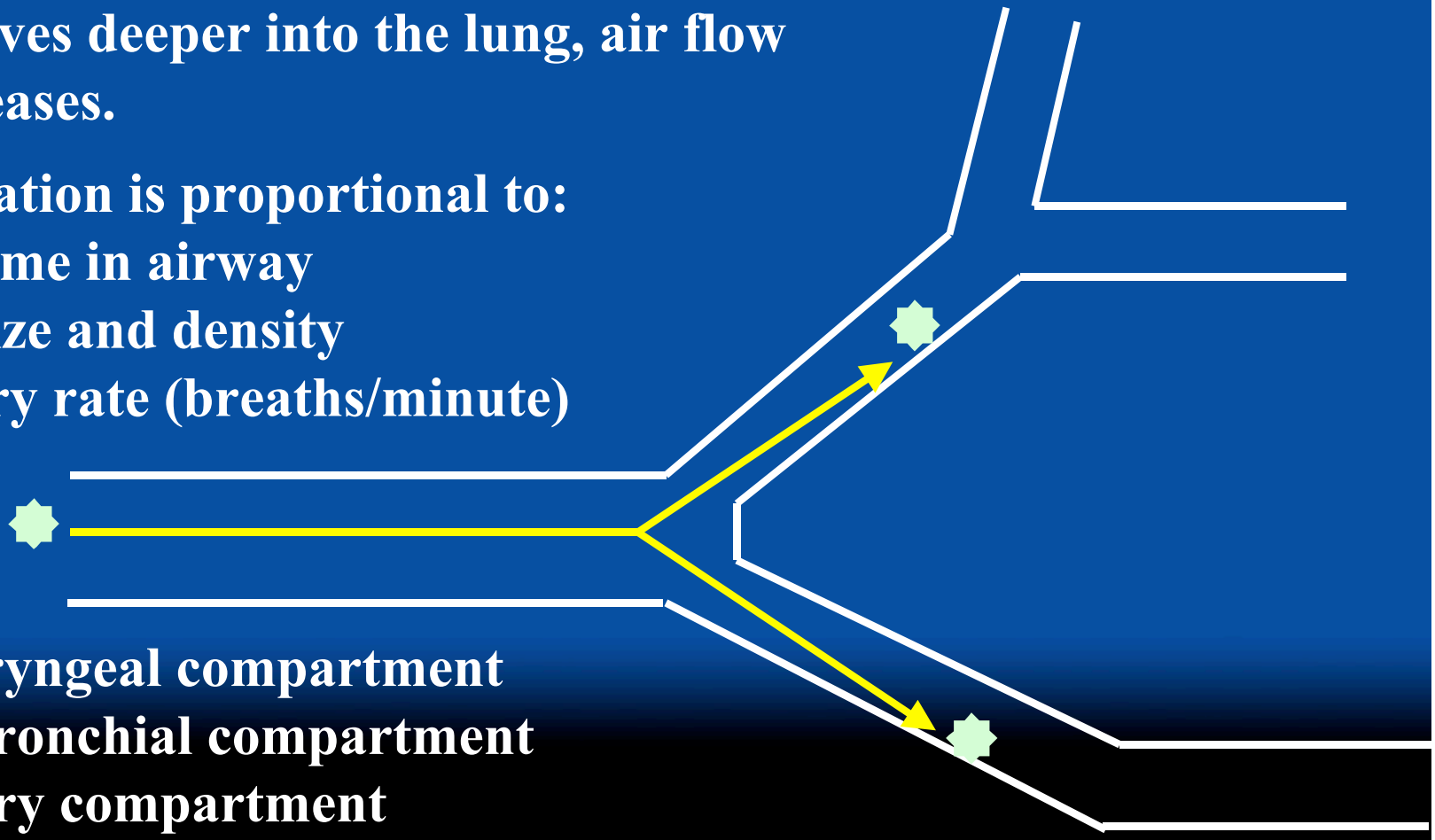


Sedimentation

When gravitational forces on a particle are greater than air resistance and buoyancy, the particle will fall out of the air stream.

As air moves deeper into the lung, air flow rate decreases.

Sedimentation is proportional to:
particle time in airway
particle size and density
respiratory rate (breaths/minute)



nasopharyngeal compartment
tracheobronchial compartment
pulmonary compartment

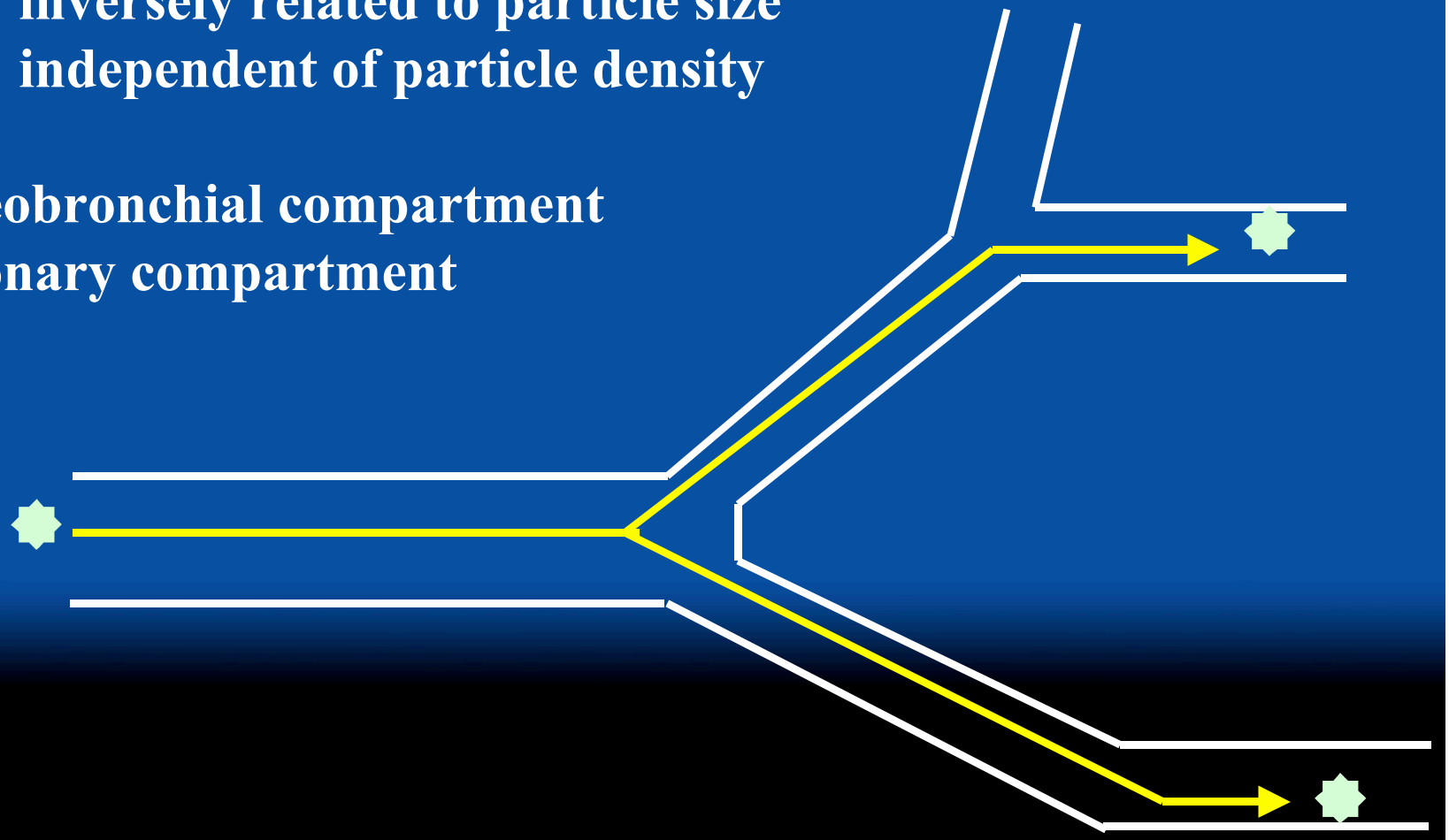
Diffusion

Particles have random motion, resulting in random impacts.

Diffusion coefficient is:

- **inversely related to particle size**
- **independent of particle density**

tracheobronchial compartment
pulmonary compartment



Electrostatic Precipitation

A minor mechanism, but may be more important for freshly generated particles because these particles tend to have greater surface charge.

Particle surface charge induces an “image” charge on lung surface.

Particle Characteristics that Affect Deposition

Size:

will effect location of deposition
sequential removal of particles as go through the lung

Particle hygroscopicity:

If a particle is hygroscopic, it can pick up water in the humidified air of the lung.

This will increase particle density and alter deposition.

Particle surface charge:

This will affect electrostatic deposition.

Ventilation Pattern can Affect Deposition

Respiratory Rate (breaths/minute)

increase respiratory rate
increase air velocity in the conducting airways
enhance impaction
decrease sedimentation and diffusion

Tidal Volume (V_T) **volume of air entering or leaving the lung in a single breath**

Increased V_T results in deeper lung penetration by particles

Person with increase V_T will likely have a decreased respiratory rate. Thus, particles stay in lung longer making deposition more likely.

Particle Clearance

Particle Clearance Mechanisms

The Nasopharyngeal Compartment

- **mucociliary clearance (transport back to nasopharynx)**
- **mechanical clearance (sneezing, coughing, swallowing)**
- **absorption into circulation (soluble particles)**

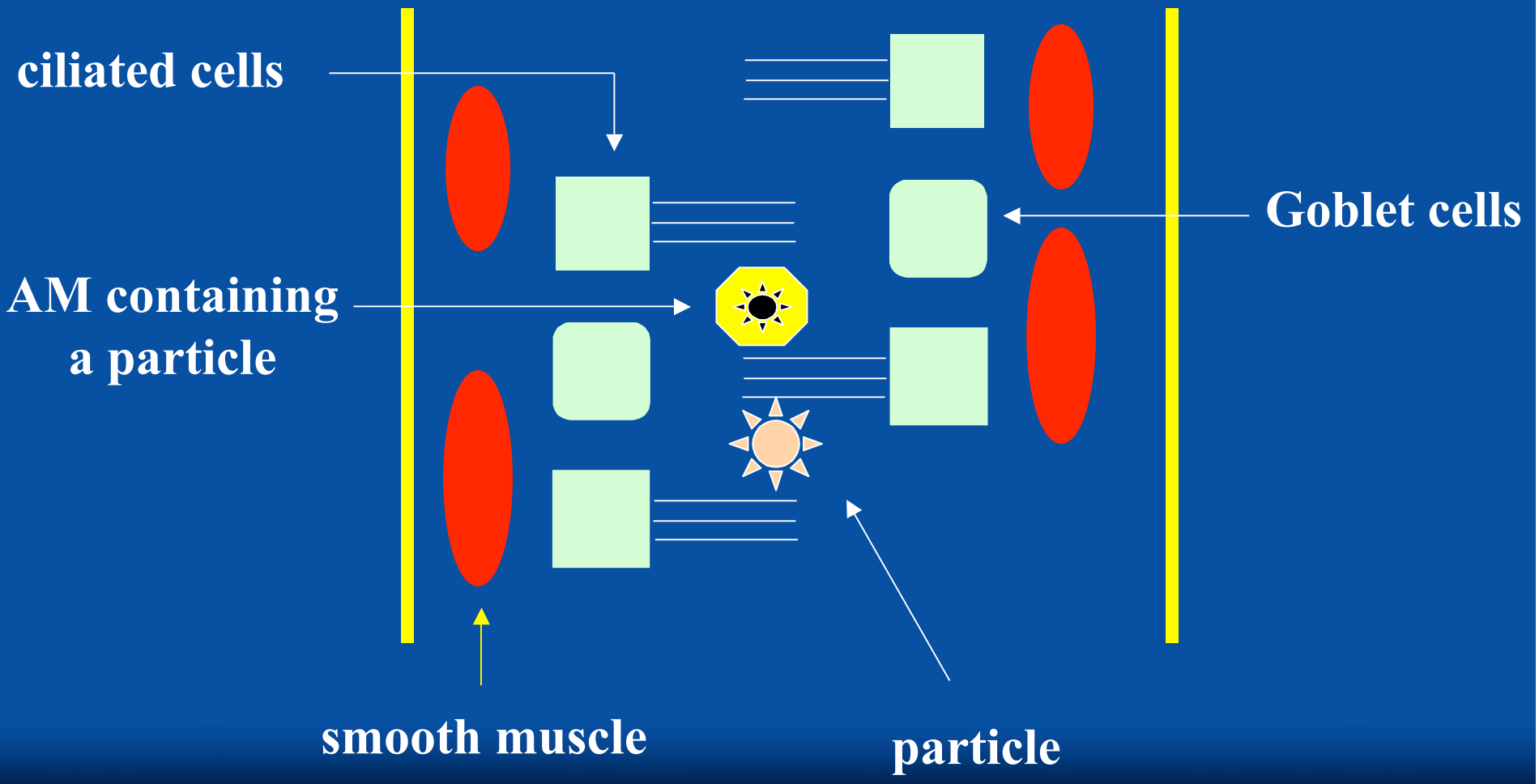
The Tracheobronchial Compartment

- **mucociliary clearance (transport to oropharynx)**
- **endocytosis into peribronchial region (insoluble particles)**
- **absorption into circulation (soluble particles)**

The Pulmonary Compartment

- **alveolar macrophage mediated clearance**
- **endocytosis by lung epithelial cells into interstitum**
- **absorption into circulation (soluble particles)**

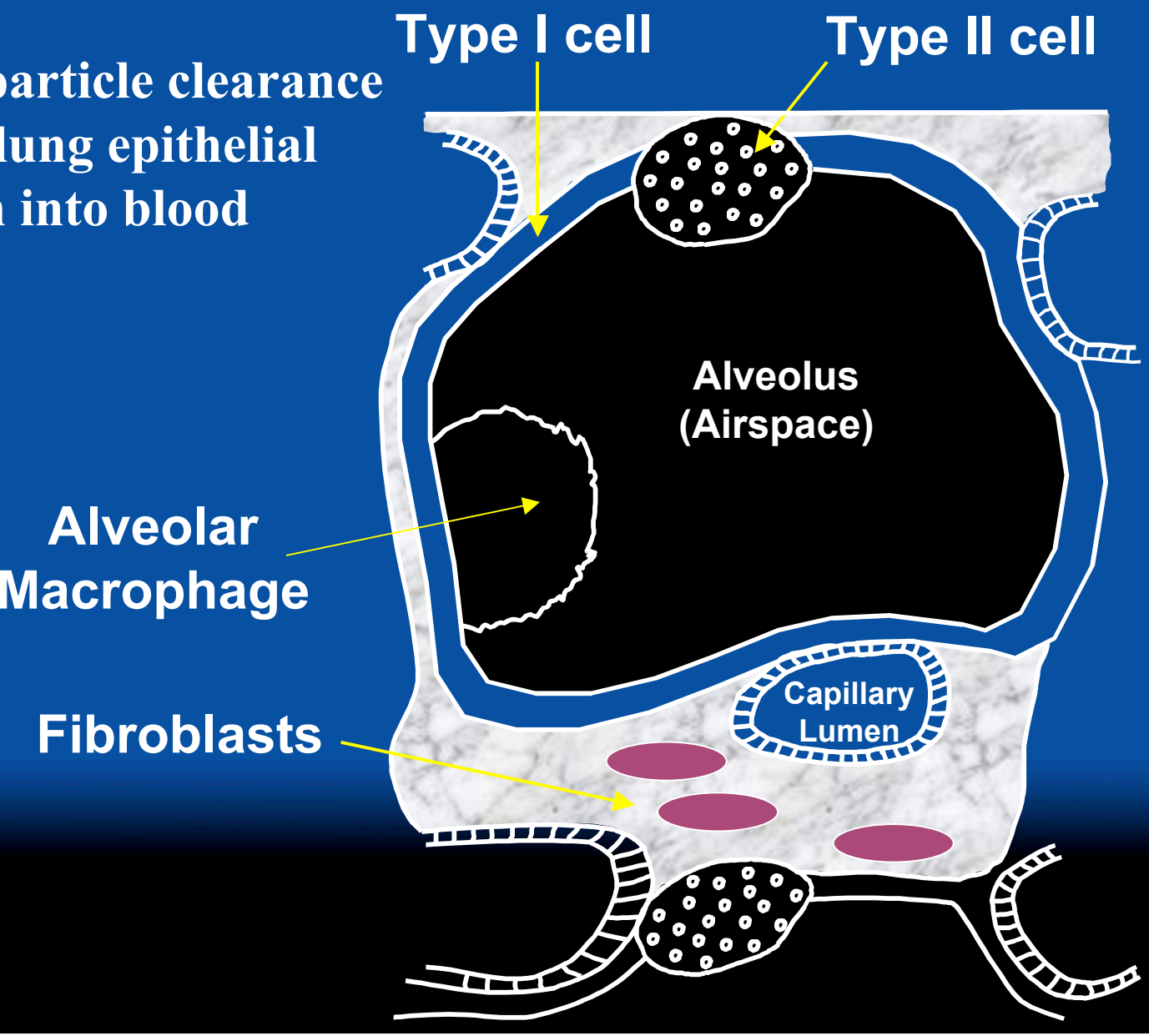
The Mucociliary Escalator



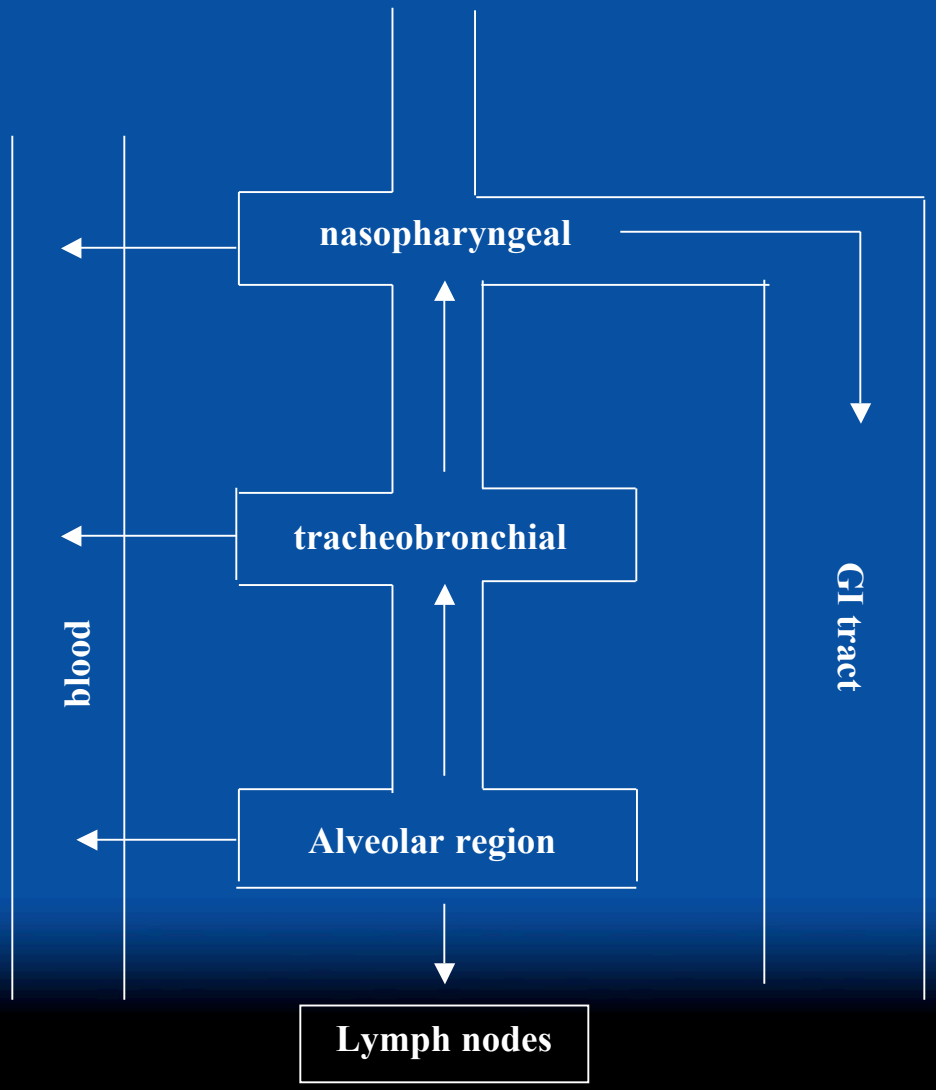
The mucocilliary escalator operates in the tracheobronchial region.

Clearance in the Pulmonary Compartment

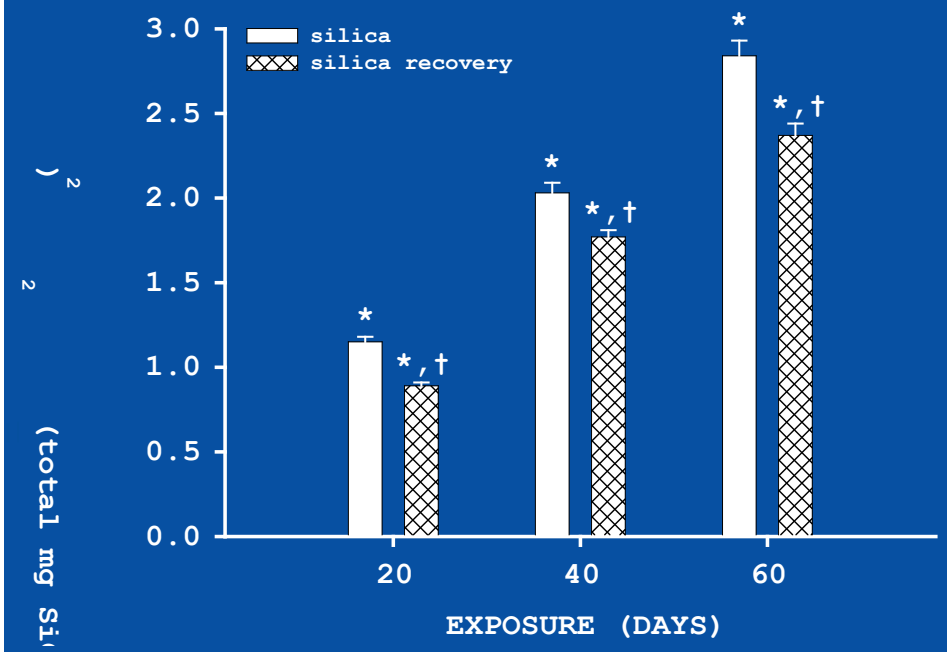
AM-mediated particle clearance endocytosis by lung epithelial cells absorption into blood

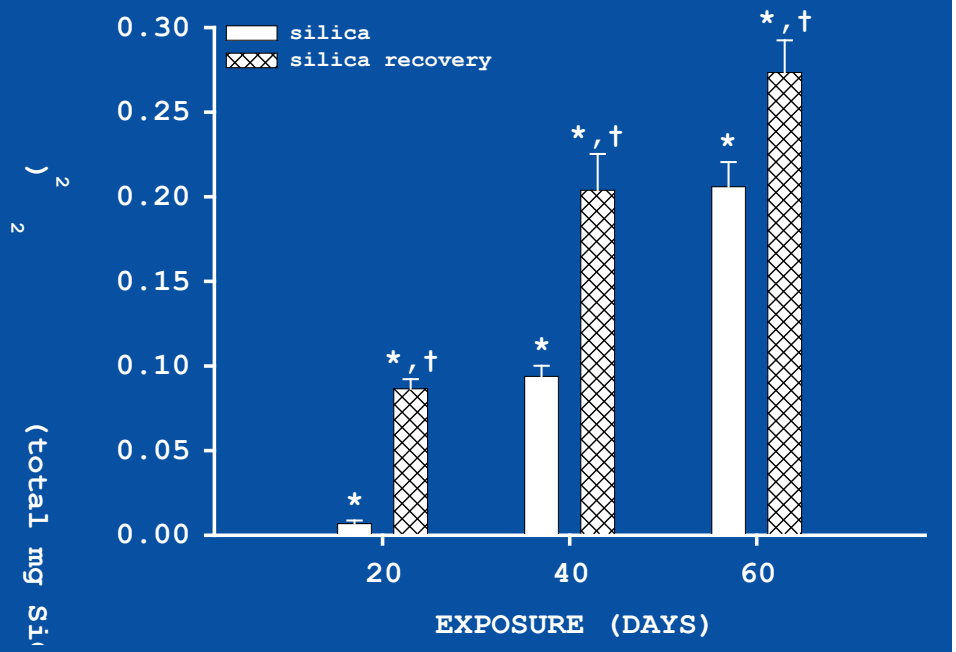


Relationships Between Clearance Mechanisms



Lung and Lymph Node Silica Burdens





As lung silica burden decreased, the lymph node silica burden increased.

Factors that Affect Particle Clearance

Gender	**no differences**
Age	**increasing age associated with decreased clearance**
Exercise	**exercise may increase clearance**
Influenza	**decreased clearance up to 3 months**
Pneumonia	**decreased clearance up to 1 year**

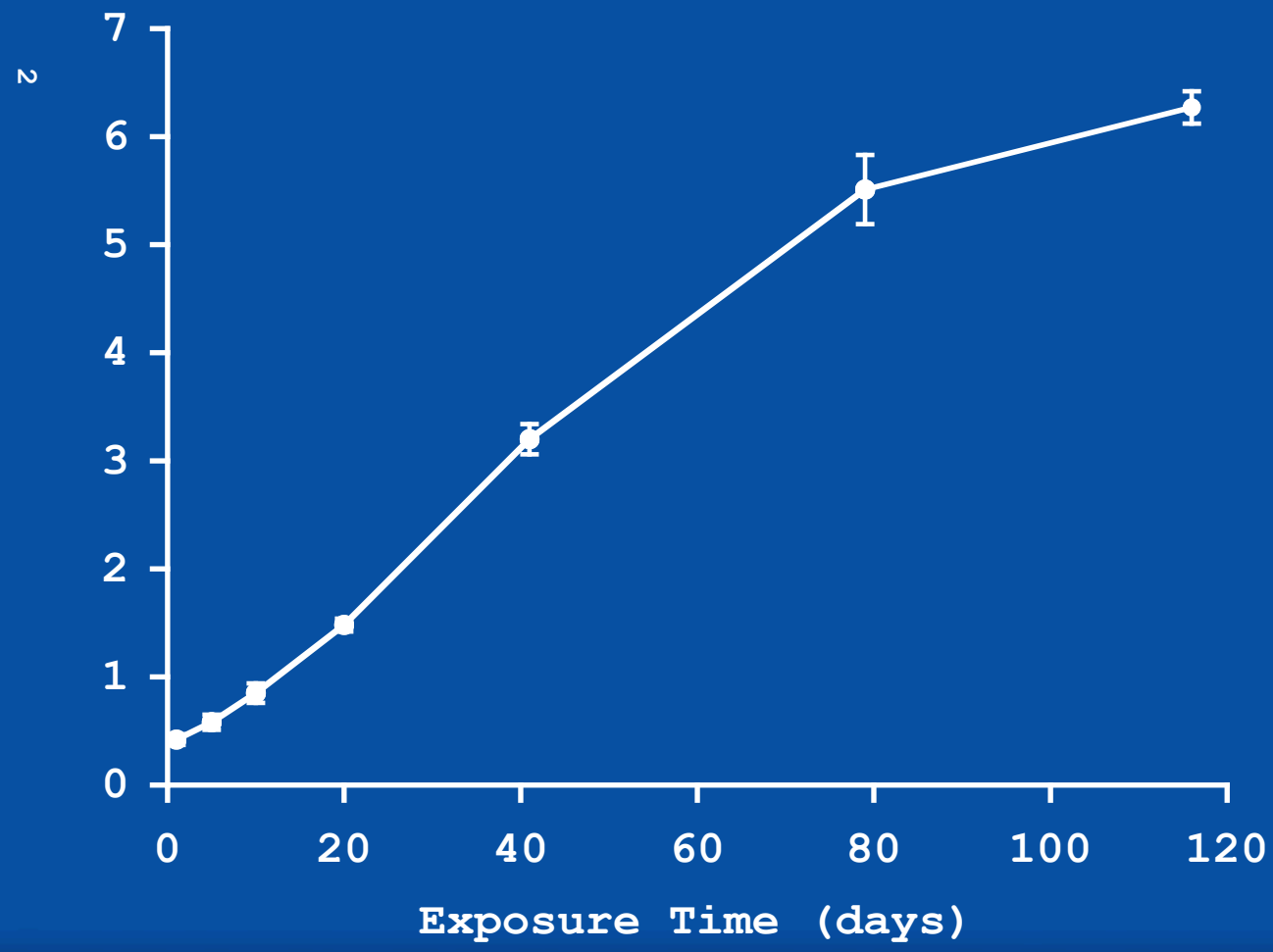
Adapted from D. Pavia et al. Bull. Eur. Physiopathol. Respir. 16, 353, 1980.

Summary of Particle Deposition and Clearance

lung compartment	deposition mechanisms	clearance mechanisms
Nasopharyngeal	impaction sedimentation electrostatic	mechanical mucociliary absorption
Tracheobronchial	impaction sedimentation diffusion	mucociliary endocytosis absorption
Pulmonary	sedimentation diffusion	AM-mediated endocytosis absorption

Metrics Used to Evaluate Particle Dose

Particle Mass Model



Dust Overloading - Defined as a condition where the mass of particles deposited reduces their clearance, and thereby increases toxicity.

Particle Volume Model

Particle volume — **It is possible to estimate the total volume of particles deposited in the lung using particle size and mass deposited.**

AM volume — **It is also possible to estimate total lung AM volume based on AM size and number of cells/lung.**

Volumetric Overloading

The volume of particles phagocytized by AMs reduces AM-mediated clearance by decreasing AM motility, thereby increasing particle toxicity.

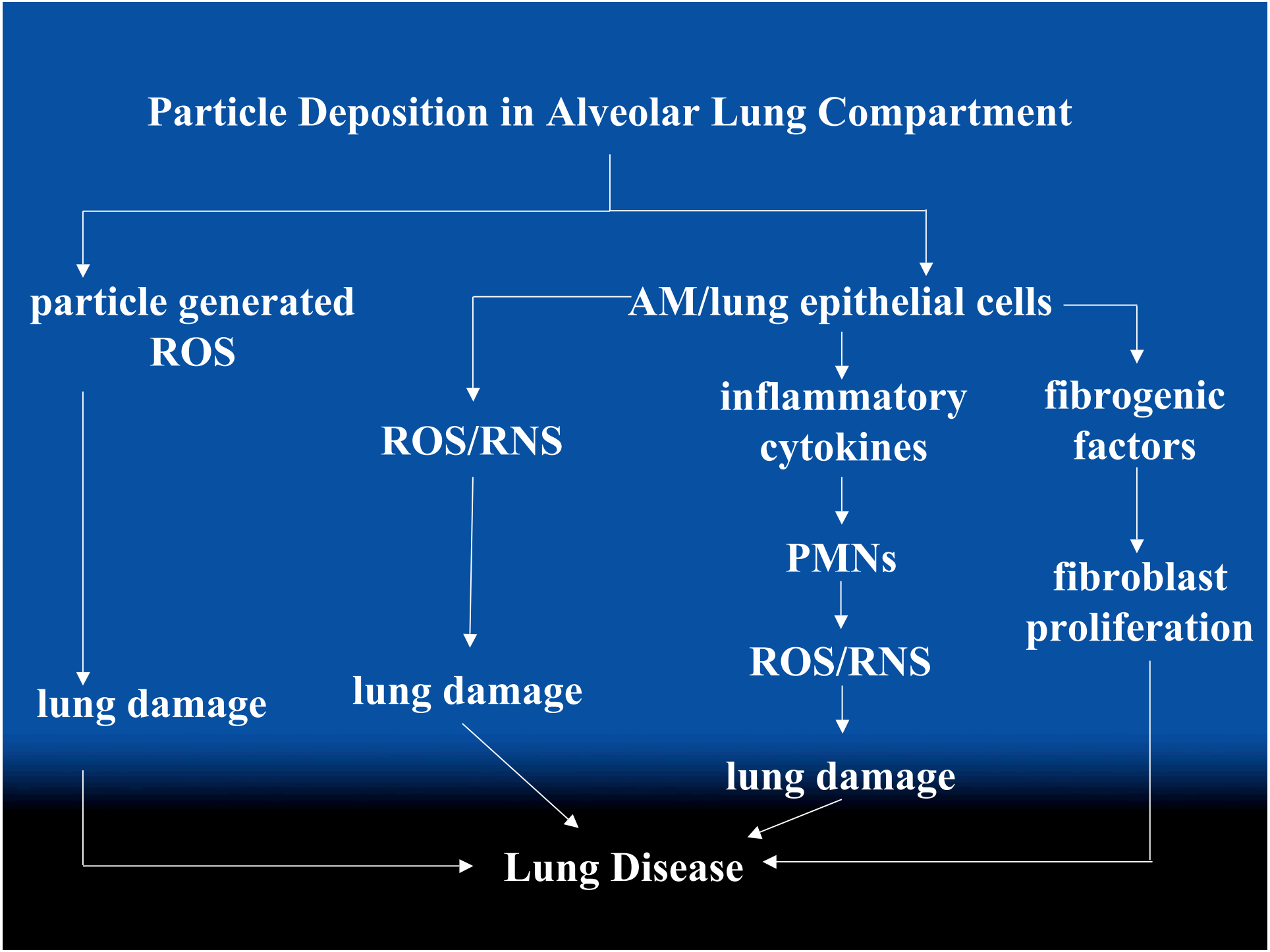
Particle Surface Area Model

Particle Surface Area

For equivalent mass doses of fine and ultrafine particles of the same composition, ultrafine particles exhibit more toxicity in comparisons to fine particles.

For equivalent particle surface areas, ultrafine particles do not exhibit more toxicity in comparison to fine particles.

General Model of Particle Toxicity in the Alveolar Lung Compartment


Particle Deposition in Alveolar Lung Compartment
particle generated ROS
AM/lung epithelial cells
ROS/RNS
inflammatory cytokines
fibrogenic factors
PMNs
fibroblast proliferation
ROS/RNS
lung damage
lung damage
lung damage
Lung Disease

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